Original Article

Clinicians as Effective Researchers

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Abstract

This article addresses the commonly asked question: Can clinicians be effective researchers?

The author draws on historical discoveries by inquisitive physicians and his own experience, which involves extensive clinical research in various aspects of pulmonary medicine in the United States and his more recent experience of overseeing the development of research at King Fahd Medical City in Riyadh, a major tertiary care center in Saudi Arabia. From this experience, the author draws conclusions as to the key aspects required for successful research. These include inquisitiveness, patience, and perseverance on the part of the clinician, along with a nurturing and supportive environment and appropriate financial, emotional, and administrative institutional support. The importance of collaboration and, finally, the need for appropriate data collection and following the Belmont principles should be emphasized.

The author strongly believes that the answer to the question "Can clinicians be effective researchers?" is a most definitive "yes."

Key words: Clinical research, history of medicine.

In December 2006, I was asked to help develop the research program at King Fahd Medical City (KFMC), a new tertiary care hospital in Riyadh, Saudi Arabia, consisting of four hospitals — general, rehabilitation, women's, children's — staffed by professionals from all parts of the world. As I began to establish the institutional review board (IRB) and plant the seeds for a research enterprise, some of the frequently heard responses were: "Why bother doing research in a clinically oriented hospital devoted to patient care?" "We are clinically oriented and do not have the expertise or know-how to do meaningful research." "We do not have the time." "We already have a job." "Give me the space and staff and I will do the research." I could add many more comments to the ones listed.

As I began to ponder the strategy to develop and answer some of these real concerns, I reflected on my own experience in the United States, where after basic medical training in Kashmir, with no experi-

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ence in research, I ended up, unplanned I might add, doing a fair amount of clinical research. Over a two-decade period, the research resulted in substantial grants and publications, including some original observations. I reflected on the studies that resulted in grants totaling more than U.S. $2.5 million from the National Institutes of Health (NIH), World Health Organization (WHO), American Lung Association, and pharmaceutical sponsors. Additionally, as chair of medicine at Nassau County Medical Center in New York, my department received an additional $4 million in grants for the state's primary care upweighting program and the HIV/AIDS Designated Center.

As I shared my experience with the interested staff at KFMC, the interest slowly started to blossom. One of the most popular presentations I made at KFMC and other institutions was "Clinicians as Effective Researchers." In this article, I will briefly outline the key characteristics of a successful clinical researcher, relying heavily upon my personal experience. Clinicians need a supportive environment within the institution and also a country that understands and invests in research and development with the anticipation of long-term benefits for the community.

The institutional and national priorities will not be addressed in detail in this article.

Individual's Role

The key element needed in a researcher is curiosity. The researcher should not be afraid to ask questions and should be willing to follow through and take chances. A few historical examples will bring home this point:

Werner Forssmann

In 1929, Werner Forssmann, 25-year-old intern from Germany, had been deeply impressed by a sketch in his physiology textbook showing a French physiologist standing in front of a horse, holding a thin tube that had been put into the jugular vein in the animal's neck and then guided into one of the heart's chambers. He could not understand why this simple technique, which would avoid the complications of opening the chest, had not already been tried on humans. Forssmann asked his supervisor, Dr. Richard Schneider, for permission to try this procedure on a terminally ill patient. The request was flatly refused, and Schneider forbade Forssmann from doing the experiment at all on any person, including himself.

Forssmann decided to do the experiment anyway, in secret. With the help of nurse Gerda Ditzen, Forssmann successfully passed a ureteral tube through a large antecubital vein into his right atrium and confirmed this historical success with a chest X-ray.[1] Thus began the era of intravascular catheterization, a procedure now taken for granted and sometimes even overused and abused, as was the case with Swanz Ganz catheter.[2] It was Werner Forssmann's curiosity, persistence, and willingness to experiment on himself that resulted in the advent of intravascular catheterization, for which he received the Nobel Prize in Physiology or Medicine in 1956.

Victor Herbert

In 1959, Victor Herbert was a 32-year-old hematologist who believed, contrary to prevailing views, that dietary deficiency alone can result in folate-deficient anemias. Sometimes, experience with a single patient can change a researcher's thinking, and that was the case with Herbert when he saw an engineer who had retired from the Boston subway system and presented with a combination of scurvy and folate-deficient megaloblastic anemia. Herbert learned that his patient, who was on a very tight budget, ate all his meals at a chain of fast-food hamburger stands in Boston. As Herbert stated: "After a diet of 15-cent hamburgers, donuts, and coffee for five years, my patient developed scurvy and megaloblastic anemia, which I believed was due to folate deficiency." To prove his hypothesis, Herbert went on a strict vitamin-deficient diet, and after 133 days of a folate-deficient diet, a weight loss of 26 pounds, a drop of hematocrit from 48-42%, and nine bone marrow examinations, Herbert developed megaloblastic anemia, confirming cause and effect.

Songtao Shi

Songtao Shi observed red tissue inside the deciduous tooth of his 6-year-old daughter. From these and other teeth Shi developed stem cells from human exfoliated deciduous teeth (SHED) at the NIH laboratories These cells have potential to develop dentin, which one day may be used to repair damaged teeth, induce regrowth of bone, and treat nerve injury or disease. This work is currently in progress.[3]

The Story of Stomach Ulcers: Acid or Bacteria?

As a student in Kashmir, I was taught that acid in the stomach is the cause of the very prevalent stomach ulcers in Kashmir. We would even provide milk via nasogastric tubes for hospitalized patients with stomach ulcers, the rationale being that the milk would neutralize the acid, which was supposed to be the cause of the ulceration. All this changed with the discovery of *Helicobacter pylori* (*H. pylori*) as a cause of stomach ulcers.

Helicobacter pylori was first discovered in the stomachs of patients with gastritis and stomach ulcers nearly 27 years ago by Barry J. Marshall and J. Robin Warren of Perth, Western Australia. At the time (1982-1983), the conventional thinking was that no bacterium can live in the human stomach, as the stomach produced extensive amounts of acid.

The bacterium had been observed in 1979 by Warren, a pathologist, who beginning in 1981 did further research on it with Marshall, a physician. After numerous unsuccessful attempts at culturing the bacteria from the stomach, they finally succeeded in visualizing colonies in 1982, when they unintentionally left their Petri dishes incubating for 5 days over the Easter weekend. In their original paper, Warren and Marshall contended that most stomach ulcers and gastritis were caused by infection by this bacterium and not by stress or spicy food, as previously assumed.[4]

To demonstrate that *H. pylori* caused gastritis and was not merely a bystander, Marshall drank a beaker of *H. pylori.* He became ill several days later with nausea and vomiting. An endoscopy 10 days after inoculation revealed signs of gastritis and the presence of *H. pylori.* These results suggested that *H. pylori* was the causative agent of gastritis. Marshall and Warren went on to show that antibiotics are effective in the treatment of many cases of gastritis. Warren and Marshall were awarded the Nobel Prize in Medicine in 2005 for their work on *H. pylori.*

Asbestos as a Carcinogen

In the 1960s Irving Selikoff documented asbestos-related diseases among industrial workers. This discovery came more or less inadvertently. In the 1950s Selikoff had opened a general medicine practice in Paterson, New Jersey. A few years later, the Asbestos Workers Union asked him to add their membership to his practice. Selikoff noticed several new cases of mesothelioma were diagnosed in a year in his practice, whereas the expected incidence was only about 5/100,000. This happened while the new cohort (asbestos workers) were still a small fraction of the clinic's patient list. This anomaly led Selikoff to examine the relationship between asbestos exposure and mesothelioma. He conducted various studies and established a link between asbestos and cancer. Asbestos-removal became a big issue; many large buildings contained tons of asbestos embedded in walls and ceilings. Controversies arose, because the workers removing the asbestos opened up intact structures, scattered toxic dust around, and left chaos behind them. Laws were passed to require better planning, preparation, and cleanup procedures. The situation eventually improved. For his pioneering work Dr. Irving Selikoff received many awards, including the Albert Lasker Award for Clinical Medical Research.

There are many examples of such astute observations by curious practicing physicians, which are highlighted in the book, *Who Goes First.*[1]

What is Research?

The common perception of research is experimenting in a laboratory. A more appropriate definition of research, in my view, is careful investigation into some subject or area of study with the aim of discovering and applying new facts or information, in short acquiring new knowledge that eventually leads to better patient care. The examples I cited above are classic cases of research, which fit this definition. One could expand the scope and do research in areas such as epidemiology, why people smoke knowing that it is harmful; why obesity is becoming so prevalent, particularly in some ethnic groups; why Saudi Arabia has the highest incidence of spinal cord injuries from road traffic accidents; why Saudis drive the way they do; why some centers have better outcome in common conditions such as myocardial infarction, stroke etc.; what is the most effective way of delivery of health care; and why, in spite of spending the largest amount of money per capita on health care in United States, the country does not have the best outcomes in objective parameters of health delivery. These are some of the many areas of great interest awaiting clinicians' research.

Two Examples from Personal Experience

Data Collection

After completing my training in medicine/pulmonary medicine, I worked in a newly established respiratory intensive care unit in Queens Hospital Center (QHC) in New York. It became apparent very quickly that a significant number of the patients admitted who became intubated were developing complications manifesting as massive gastrointestinal (GI) bleeding, renal failure, nosocomial infections, and tracheal complications from endotracheal tubes and tracheostomies. To develop data regarding the incidence, causes, and impact on morbidity and mortality of these complications, with the help of the cooperative nursing staff and an investment of 85 cents in a notebook, we recorded all admissions and marked any complications that developed. At the end of the week, I analyzed this data, and over a month's admission of 25 to 30 patients we would have a few GI bleeders and a few with other complications. Gradually, over a period of several months, we had data on hundreds of patients and, during my stay at QHC, I accumulated data on more than 3,000 patients. The nursing staff did the data entry, while I reviewed the accumulated data. There was no protected time in a busy public hospital. We found an incidence of more than 10% with massive GI bleeding, requiring a transfusion of two or more units of blood. To reduce the incidence of GI bleeding, we adopted a gastric neutralization program, initially with antacids and later on with H2 blockers, with dramatic improvement. We reported the largest series on this subject.[5] We had similar experience in addressing complications of renal failure, and tracheal complications. After presenting our findings at national meetings, we were asked to write a monograph on the subject.[6] The take-home message from this experience is that you need to have accurate reliable transparent data and from such accumulated experience one can make interesting observations, which can lead to better patient care.

Lengthy Investigation and Research

In mid 1980s I served as an external examiner for the medical school in Amman, Jordan. One of the short cases presented was that of a boy in his teens with classic saccular bronchiectasis. The diagnosis was obvious, and the students had no difficulty in describing the clinical findings. However, later that evening, Professor Naif Sliman posed the following question: "The case of bronchiectasis you saw today is rather unusual in that he and several of his brothers have the same problem, and they are challenged intellectually. The sisters and other siblings do not have this problem, can you help us sort this out?"

It was clear that there was some inherited genetic disorder affecting some, but not all, male siblings in this rather large Palestinian family of 14-plus siblings. We went through the usual differential diagnosis, did the chromosome analysis, studied the cilia from the affected patients, and conducted other routine investigations. The affected family was living in a refugee camp in Jordan, and I was in New York. This created many interesting challenges in logistics. We had to seek the assistance of experts from diverse fields involving genetics, ciliary sampling, and motility studies. After 15 years of collaboration and work with many investigators in Amman as well as in the United States in Atlanta, Georgia; Stony Brook, New York; and Charleston, South Carolina, we were able to identify a new inherited genetic disease.[7] The lessons learned from this experience are that investigation and research can take a long time. One needs to be patient and, most important, one needs to collaborate with the appropriate investigators within and outside the parent institution. This study "research" took 15 years.

Ethics in Research

After serving on the board of the professional medical conduct in New York, it became apparent to me that physicians are not immune to ethical lapses. This becomes even more important in research where patients are entrusting the physicians to being tested with an unproven, often not approved, medication or device. Two personal examples will highlight this.

a) I did sizable clinical research in the application of fluoroquinolones in respiratory tract infections. As our team published and presented our findings in professional meetings I began to receive requests from several different pharmaceutical companies to test their brand of fluoroquinolones. One such product had obvious neurologic complications, every third or fourth of my enrolled patients had some evidence of neurologic stimulation: irritability, sleeplessness, and even seizures. I felt exposing my patients to such side effects was not appropriate and quickly informed my IRB that I was canceling the study.

b) While studying Ciprofloxacin, which had been showing excellent clinical results,[8] one of our enrolled patients had a grand mal seizure, which she never had before. After careful clinical investigation, we determined it was most likely the result of a very high blood theophylline level resulting from the interaction between the Ciprofloxacin and theophylline. Up to that time, Ciprofloxacin had not been known to increase the blood theophylline level. The sponsoring company was quickly advised of this complication, and, to its credit, it encouraged us to study this interaction in greater detail, which we did and thus established the Cipro-theophylline interaction.[9]

The point of these two examples is that because complications can occur while doing research, it is the investigators' responsibility and moral/ethical duty to weigh the risk/benefit ratio carefully, keeping the patients' interest and well-being uppermost in mind.

Dr. Stephen E. Straus is a highly respected researcher at the NIH. He was the principal researcher in a research study on a new investigational drug for the treatment of hepatitis. Five patients he treated at the NIH hospital in Bethesda, Maryland, died, which led to news reports and congressional hearings. The study was discontinued, and eventually he and his colleagues were cleared of any wrongdoing. Later on they found out that the investigational drug was a mitochondrial poison leading to severe metabolic acidosis. Straus regularly presents this incident at the annual NIH course on research. Understanding the importance of unanticipated risks in clinical research is highly recommended for all who do clinical research.[10]

Financial Support

Developed countries have recognized that support for research and development pays rich dividends in the long run. The amount invested in research and development in Japan is 2.9% of the gross domestic product (GDP). In the United States and Europe, it averages between 1.5% and 3% of the GDP. The Southeast Asian countries average 0.89% of their GDP, and in the Arab countries it averages only 0.23% of the GDP, with the exception of Qatar, where the percentage is 2.8%. These numbers translate to $19 per person in Saudi Arabia, $665 per person in the United States, and $649 per person in Japan. In developed countries, the private sector plays a major role in supporting research and development. For example in the United States, the government provides the NIH with an annual budget of around $28 billion, whereas the private sector support for research in the United States is estimated to be double that amount.

A good example of the rich returns for research investment are evident with the recent epidemic of HIV/AIDS, which in the mid 1980s had no treatment and had a very high mortality rate. If this trend had continued, it is estimated that in the United States we would have more than 200,000 hospital beds occupied by AIDS patients. Thankfully, with an investment of $10 billion dollars over 10 years the virus was identified, drugs were discovered, and the treatment of this deadly disease changed from inpatient treatment to outpatient long-term care. Thus the $10 billion investment saved $1.4 trillion in health-care costs, or a 1:140 return.[11]

Summary

Based on the author's personal experience as a clinical researcher and having overseen the expanding research at KFMC since 2007, where the submissions of research proposals have grown from 27 in 2007 to 62 in 2008. Submissions are projected to reach close to 100 in 2009. The key factors for success in research are intellectual curiosity; asking the key questions; "but why," persistence; follow up to test hypotheses; honesty and integrity in collecting data; reporting all findings, both the expected and the unexpected; assessing what is available and doable in the place you work, as there is no point in doing research in transplantation if your institution does not have a transplant program; and most of all, learning to collaborate and cooperate.

On top of that, there is an element of luck involved, being in the right environment, having access to role models, and having a helpful mentor and cooperative peers.

Follow Up

All of the good work is of little value if it does not get presented or published so the results of the investigators' work can be shared with a larger community. Here are a few suggestions in getting the material published:

The qualities of the manuscript and the journal must match; evaluate journal quality by its editorial office, publishing, and distribution factors; read the instructions to authors carefully; and novelty, creativity, and level of interest are important factors. The abstract you submit must have all key findings and elements listed; check for methodological quality; register human studies/clinical trial; place your findings in perspective; ensure clarity of presentation; avoid paucity of data; check the appropriateness of the statistical methods; emphasize the clinical significance of the study; and, most important, do not get disheartened if you receive a rejection. The rate of acceptance in high-impact journals can be as low as 10-15% of all submissions. I have had my share of rejections over the years.

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